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TRANSMITTAL FORM

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Total Number of Pages in This Submission

Application Number	09/897,584
Filing Date	06/29/2001
First Named Inventor	Robert S. DeWitte et al
Art Unit	1631
Examiner Name	Cheyne Ly
Attorney Docket Number	42697.265US3

ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
- ☒ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☒ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☒ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☒ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☒ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☑ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☒ Proprietary Information
- ☒ Status Letter
- ☑ Other Enclosure(s) (please Identify below):
  - Postcard

Remarks

-Cover Letter
- Copy of Non-Compliance
- Appendix A-E

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Wilmer Cutler Pickering Hale and Dorr LLP		
Signature	Wayne K		
Printed name	Wayne M. Kennard		
Date	5/03/2005	Reg. No.	30,271

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

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In the United States Patent and Trademark Office

Applicant(s)	Robert S. DeWitte et al
Serial No.	09/897,584
Filed	June 29, 2001
Title	System and Method for Structure-Based Design That Includes Accurate Predication of Binding Free Energy
Examiner	Cheyne Ly
Unit	1631

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1440
Alexandria, VA 22313-1450

SIR:

Pursuant to the Notification of Non-Compliance dated April 6, 2005, please replace the Appeal Brief that was filed on October 7, 2004 and January 13, 2005 with the Appeal Brief that is enclosed. The items pointed out in the Notification have been addressed. This Brief is filed in triplicate.

Respectfully submitted,

Dated: May 3, 2005

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Notification of Non-Compliant Appeal Brief (37 CFR 41.37)	Application No.	Applicant(s)	
	09/897,584	DEWITTE ET AL.	
	Examiner	Art Unit	
	Cheyne D. Ly	1631	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

The Appeal Brief filed on *13 January 2005* is defective for failure to comply with one or more provisions of 37 CFR 41.37.

To avoid dismissal of the appeal, applicant must file a complete new brief in compliance with 37 CFR 41.37 within **ONE MONTH or THIRTY DAYS** from the mailing date of this Notification, whichever is longer. **EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136.**

1. ☒ The brief does not contain the items required under 37 CFR 41.37(c), or the items are not under the proper heading or in the proper order.

2. ☐ The brief does not contain a statement of the status of all claims, (e.g., rejected, allowed or confirmed, withdrawn, objected to, canceled), or does not identify the appealed claims (37 CFR 41.37(c)(1)(iii)).

3. ☐ At least one amendment has been filed subsequent to the final rejection, and the brief does not contain a statement of the status of each such amendment (37 CFR 41.37(c)(1)(iv)).

4. ☐ (a) The brief does not contain a concise explanation of the subject matter defined in each of the independent claims involved in the appeal, referring to the specification by page and line number and to the drawings, if any, by reference characters; and/or (b) the brief fails to: (1) identify, for each independent claim involved in the appeal and for each dependent claim argued separately, every means plus function and step plus function under 35 U.S.C. 112, sixth paragraph, and/or (2) set forth the structure, material, or acts described in the specification as corresponding to each claimed function with reference to the specification by page and line number, and to the drawings, if any, by reference characters (37 CFR 41.37(c)(1)(v)).

5. ☐ The brief does not contain a concise statement of each ground of rejection presented for review (37 CFR 41.37(c)(1)(vi))

6. ☒ The brief does not present an argument under a separate heading for each ground of rejection on appeal (37 CFR 41.37(c)(1)(vii)).

7. ☐ The brief does not contain a correct copy of the appealed claims as an appendix thereto (37 CFR 41.37(c)(1)(viii)).

8. ☐ The brief does not contain copies of the evidence submitted under 37 CFR 1.130, 1.131, or 1.132 or of any other evidence entered by the examiner and relied upon by appellant in the appeal, along with a statement setting forth where in the record that evidence was entered by the examiner, as an appendix thereto (37 CFR 41.37(c)(1)(ix)).

9. ☐ The brief does not contain copies of the decisions rendered by a court or the Board in the proceeding identified in the Related Appeals and Interferences section of the brief as an appendix thereto (37 CFR 41.37(c)(1)(x)).

10. ☒ Other (including any explanation in support of the above items):

In section VII, Appellant identities items (3) and (4) as different issues corresponding to different grounds of rejection on appeal. However, Appellant does not present an argument under a separate heading for each ground of rejection as required. It is noted that Appellant presents arguments (page 7) directed to items (3) and (4) under the same heading which causes the instant Appeal Brief to be non-compliant .

Ardin H. Marschel 4/3/05

ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER

hc

In the United States Patent and Trademark Office

Applicant(s)	Robert S. DeWitte et al
Serial No.	09/897,584
Filed	June 29, 2001
Title	System and Method for Structure-Based Design That Includes Accurate Predication of Binding Free Energy
Examiner	Cheyne Ly
Unit	1631

CERTIFICATE UNDER 37 C.F.R. § 1.10

I hereby certify that the attached papers are being deposited with the United States Postal Services as "Express Mail Post Office to Addressee" Mailing Label No. EV390708005 US addressed to: Mail Stop Appeal Brief – Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below

on 5-3, 2005. Susie Fernandez

Susie Fernandez

APPEAL BRIEF UNDER 37 C.F.R. §1.192

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SIR:

This is an Appeal Brief pursuant to the Notice of Appeal filed April 7, 2004, appealing the rejection of claims 1-4 in the Office Action dated October 8, 2003. This Brief is filed in triplicate.

I. REAL PARTY IN INTEREST

The real party in interest is Harvard University, 124 Mount Auburn Street, Cambridge, MA 02138, the assignee of the above-identified application.

II. RELATED APPEALS AND INTERFERENCES

The Appellants, the Appellants' legal representatives, and the Assignee are not aware of any pending appeals or interferences that would directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

III. STATUS OF THE CLAIMS

Claims 1-4 are pending in the present application. Claims 5-20 have been cancelled based on Appellant's election to prosecute the Group I claims, claims 1-4, in response to a Restriction Requirement dated September 26, 2002. Claims 1-4 have been twice rejected under 35 U.S.C. §§ 112, 1st paragraph, 102 in light of U.S. Patent No. 5,495,423 to DeLisi et al. ("DeLisi"), and 103 in light DeLisi in view of *In Re Gulack*, 703 F. 2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983) ("*Gulack*") or DeLisi in view of U.S. Patent No. 6,251,620 to Hatada et al. ("Hatada"). These rejections to claims 1-4 are appealed.

IV. STATUS OF AMENDMENTS

Claims 1-4 were first rejected in the Office Action dated May 12, 2003. In the Reply filed August 8, 2003, Appellants amended pending claim 1 to overcome the Examiner's bases for rejection. The Examiner issued a second rejection of claims 1-4 in the Office Action dated October 8, 2003. Appellants filed a Reply dated April 4, 2004 to the Office Action dated October 8, 2003, in which Appellants addressed the Examiner's bases for rejecting amended claims 1-4 without further amendment to claims 1-4. There were no further amendments to the claims.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention is directed to a novel system and method for structure-based drug design that may be carried out by the de novo design of molecules that bind to a receptor site on a protein. Of the pending claims, claim 1 is an independent claim and claims 2-4 depend from claim 1.

Claim 1 recites an eight step method for carrying out the present invention.[1] According to claim 1, the de novo method of designing molecules that bind to a receptor site on a protein includes (1) building the molecules at the site by adding successive random molecular fragments

[1] See Appendix C for a full version of amended claim 1.

to an initial molecular fragment, and then determining the molecular fragment that is best to use whether or not it results in a "free energy estimate for the molecule that may be higher than the lowest free energy estimate possible for the molecule," (2) repeating the first step to generate a collection of molecules and ranking the collection according to the free estimates, (3) select a high ranking molecule and build a second generation molecule, (4) minimize the protein /ligand using an empirical force field, (5) measuring the empirical interaction energy of the second generation molecules and ranking them according to specific criteria, (6) modifying the second generation molecules which includes atomic and/or functional substitutions, initiating growth from a specific receptor site, and solubility-enhancing measures, (7) repeating the processes to obtain a high ranking second-generation molecule at both steps (5) and (6), and (8) displaying the second-generation molecule identified at step (7). [Specification: Page 16, line 2 to Page 17 line 10; Page 20, line 17 to Page 21 line12; Page 24, lines 5-13]

Claims 2-4 add further limitations to claim 1. Claim 2 recites the preferred group of receptor sites for use in the method of the present invention. [Specification: Page 17, line 11-14] Claim 3 specifies that the empirical interaction energy comprises CHARMM interaction energy. [Specification: Page 17, lines 14-15] And claim 4 specifies that the empirical force field comprises CHARMM. [Specification: Page 17, lines 14-15] (See Appendix C, claims 2-4).

A significant aspect of the present invention is that in building the final molecule, the building steps include using molecular fragments that do not have the lowest free energy estimate, which is truly counterintuitive. The result is a novel system that provides rapid de novo drug design.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1-4 were first rejected in the Office Action dated May 12, 2003. In that Office Action, the Examiner rejected claims 1-4 on the following bases:

A. 35 U.S.C. § 101 for the claimed invention allegedly being directed to non-statutory algorithm-type subject matter;

B. 35 U.S.C. § 112, 1st paragraph, for the specification allegedly not providing enablement for de novo designs of molecules that interact with any receptor other than Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, or human carbonic anhydrase II protein;

C. 35 U.S.C. § 102 for allegedly being anticipated by DeLisi;

D. 35 U.S.C. § 103 for allegedly being obvious in light DeLisi in view *Gulack*; and

E. 35 U.S.C. § 103 for allegedly obvious in light of DeLisi in view Hatada.

The Examiner issued a second rejection of claims 1-4 in the Office Action dated October 8, 2003. In that Office Action, the Examiner rejected amended claims 1-4 on the following bases:

A. 35 U.S.C. § 112, 1st paragraph, for allegedly not being enabling for de novo design of molecules that interact with any receptor;

B. 35 U.S.C. § 102 for allegedly being anticipated by DeLisi;

C. 35 U.S.C. § 103 for allegedly being obvious in light DeLisi in view *Gulack*; and

D. 35 U.S.C. § 103 for allegedly obvious in light of DeLisi in view Hatada.

Appellants request that the Board review on Appeal and overturn the Examiner's basis of rejection set forth in the Office Action dated October 8, 2003.

A copy of amended claims 1-4 is set forth in Appendix A. For the Board's convenience, a copy of the May 12, 2003 Office Action is attached at Appendix B, Appellants' August 8, 2003 Reply is attached at Appendix C, the October 8, 2003 Action is attached at Appendix D, and Appellants' April 4, 2004 Reply is attached at Appendix E.

VII. ISSUE

Appellant, contrary to the contentions of the Examiner, submits that amended claims 1-4 are (1) enabling under 35 U.S.C. § 112, 1st paragraph for de novo design of molecules that interact with any receptor; (2) are not anticipated by DeLisi under 35 U.S.C. § 102, (3) are not obvious in light DeLisi in view *Gulack* under 35 U.S.C. § 103, and (4) are not obvious in light of DeLisi in view Hatada under 35 U.S.C. 103.

VIII. GROUPING OF CLAIMS

Claims 1-4 are presented on appeal and the respective claims do not stand or fall together. Each of the claims recites a distinct set of method steps that is separately patentable from the other claims. .

IX. ARGUMENT

A. Claims 1-4 are Enabled for De Novo Drug Design

The Examiner rejected claims 1-4 under 35 U.S.C. § 112, first paragraph, on the basis that they are enabled only for de novo design of molecules that interact with receptor sites of

Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, or human carbonic anhydrase II protein, but not for the de novo design of molecules that interact with any receptor. The receptor sites that have just been recited are the preferred receptor sites. (See, Specification page 60, lines 8-11). These examples of receptor sites are the best mode for carrying out the invention at the time the application was filed.

The best mode and enablement requirements are two separate and distinct requirements under 35 U.S.C. § 112, first paragraph. *Teleflex, Inc. v Ficosa North America Corp.*, 299 F.3d 1313 (Fed. Cir. 2002). The best mode in the form of examples in the present application appear to be read by the Examiner as limitations to the scope of the claims and any receptor sites beyond them are not enabled. The case law, however, is clear that it is improper to limit the scope of claims to the preferred embodiment unless such a limitation is set forth in the specification or prosecution history. (See, *Northern Telecon Ltd. v. Samsung Electronics Co.*, Ltd., 215 F.3d 1281 (Fed. Cir. 2000); *TurboCare Division of Demag Delaval Turbomachinery Corp., v. General Electric Co.*, 264 F.3d 1111 (Fed. Cir. 2001)). Appellants have not so limited the claims and, as such, the claims will have a scope that is supported by the specification beyond the preferred receptor sites.

The Specification at page 59, line 11 to page 60, line 8 describes the method of evaluating a receptor site for de novo design. Appellantss describe at the bottom of page 22 and the top of page 23, which crystalline structures of proteins and protein-ligands can be disassembled and the free energy contributions determined. This process is known and well within the capabilities of one skilled in the art without undue experimentation. Thus, the method of the present invention would result in the receptor sites that include, but would not be limited to, the preferred receptor sites Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, or human carbonic anhydrase II protein. Accordingly, the receptor sites that meet the criteria set forth by this method would be enabled by the disclosure of the present application beyond the preferred receptor sites. Thus, the pending claims are enabled by the specification beyond just the preferred receptor sites according to the disclosed method for evaluating the receptor sites to determine each's appropriateness for use. (See, *Mycogen Plant Science, Inc. v. Monsanto Co.*, 252 F.3d 1306 (Fed. Cir. 2001)). Accordingly, the enablement rejection has been traversed and should be withdrawn.

B. Claims 1-4 are not Anticipated by DeLisi

The Examiner has rejected claims 1, 3, and 4 under 35 U.S.C. §102 for anticipation based DeLisi. The standard for sustaining a rejection for anticipation is that a single prior art reference must disclose each and every limitation of the claim. *See*, e.g., *Schering Corp. v. Geneva Pharms., Inc.,* 339 F.3d 1373, 1377 (Fed. Cir. 2003; *Trintic Industries, Inc. v. Top-USA Corp.*, 295 F.3d 1292-1295 (Fed. Cir 2002); *Brown v. 3M*, 265 F.3d 1349-1351 (Fed. Cir. 2001). DeLisi, however 'does not meet this standard.

Claim 1, as amended, recites that the method uses "second generation molecules from one or more functional groups of the high-ranking molecules determined at Steps (a) and (b). Claim 1 also recites at Step (a) that there is the selection of fragments and their orientation is predicated on a free energy estimate that "may be higher than a lowest free energy estimate possible for the molecule." The Examiner has contended that DeLisi discloses the use of second-generation molecules in its process and this method of fragments for the molecule. However, a review of DeLisi does not support these contentions. This is a first basis for traversing the Examiner's anticipation rejection.

Claim 1 recites a method that includes Steps (a) and (b) that are directed to the first selection and ranking of molecules, and Steps (c)-(h) directed to the second-generation molecules that are derived from one or more functional groups of the high-ranking molecules determined at Steps (a) and (b). The generation of the resultant molecules will be based on the use of a "free energy estimate for the molecule that may be higher than the lowest free energy estimate possible for the molecule." DeLisi does not disclose or suggest in any way the method of claim 1 that builds a first collection of molecules and then builds second-generation molecules from one or more functional groups of the high-ranking molecules of the first collection based on the use of a "free energy estimate for the molecule that may be higher than the lowest free energy estimate possible for the molecule." Moreover, during the prosecution up to this point, the Examiner has failed to show that DeLisi anticipates these features of claim the present invention. Therefore, DeLisi does not teach or suggest at least two elements of claim 1. As such, DeLisi, with any candor, cannot be relied on to teach each and every element of claim 1 in the same way as is necessary for DeLisi to sustain an anticipate rejection under 35 U.S.C. § 102. This is a second basis under which Appellants traverse the Examiner's anticipation rejection.

Claims 2-4 depend from claim 1, and, as such, each contain all of the features of claims 1. Since DeLisi does not anticipate claim 1 as demonstrated above, claims 2-4 are not anticipated for the same reasons.

C. Claims 1-4 are not Rendered Obvious by DeLisi/Gulack

The Examiner has rejected claims 1-4 under 35 U.S.C. §103 for obviousness based DeLisi. in view of *In re Gulack*, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983). The legal standard for a finding of obviousness based on a combination of prior art references is that there must be some "reason, suggestion, or motivation in the prior art...that would lead one of ordinary skill in the art to combine the references." *Riverwood Int'l Corp. v. Mead Corp.*, 212 F3d 1365, 1366 (Fed. Cir. 2000), cert. denied, 531 US 1012 (2000) *Ruiz v. A.B. Chance Company Co.*, 234 F3d 654, 664 (Fed. Cir. 2000). When obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of the reference to demonstrate the claimed invention. *B.F. Goodrich Company v. Aircraft Breaking Sys. Corp.*, 72 F3d 1577, 1582 (Fed. Cir. 1996).

The Examiner in applying *Gulack* to the DeLisi states that the case stands for defining that nonfunctional descriptive material will not distinguish the invention from prior art in terms of patentability. Therefore, it is as if the Examiner has applied DeLisi as a single reference in rendering the claims obvious.

Although Appellants believe the Examiner was in error with regard to the conclusion reached regarding the distinguishing features of the "second generation molecule," Appellants want to point out, as was set forth in the previous section on anticipation, that claim 1 also recites that the selection of fragments and their orientation is predicated on a free energy estimate that "may be higher than a lowest free energy estimate possible for the molecule." This is clearly not a "nonfunctional descriptive material" that distinguishes claim 1 from the Examiner's basis for his obviousness rejection, but is clearly part of the defined claimed method for generating the first and second-generation molecules. Neither DeLisi nor the application of the *Gulack* principles to DeLisi's teachings in any way render claim 1 obvious. Therefore, Appellants request the obviousness rejection be withdrawn as it has been applied to this claim.

Claims 2-4 depend from claim 1. These claims add features to claim 1 and include its method of building molecules that use free energy estimates that may be higher than a lowest free energy estimate possible for the molecule. Therefore, these claims are not rendered obvious

by the DeLisi in view of *Gulack* for the same reason as claim 1 is not obvious. Appellants respectfully request that the obviousness rejection be withdrawn as it has been applied to claims 2-4 based on DeLisi in view of *Gulack.*

D. Claims 1-4 are not Rendered Obvious by DeLisi/Hatada

The Examiner has also rejected claims 1-4 for obviousness based on the combination of DeLisi in view of Hatada. As stated, the legal standard for a finding of obviousness based on a combination of prior art references is that there must be some "reason, suggestion, or motivation in the prior art...that would lead one of ordinary skill in the art to combine the references." *Riverwood Int'l Corp. v. Mead Corp.*, 212 F3d 1365, 1366 (Fed. Cir. 2000), cert. denied, 531 US 1012 (2000) *Ruiz v. A.B. Chance Company Co.*, 234 F3d 654, 664 (Fed. Cir. 2000).

The Examiner cited Hatada for allegedly teaching that three-dimensional structures of SH2 domain protein have been determined by X-ray crystallography. However, the Examiner has not demonstrated that there is a suggestion in DeLisi that teaching of Hatada should be combined with it as is necessary for the two references to be properly combined to form an obviousness rejection. This is a first basis why the combination of DeLisi in view of Hatada does render claim 1, or claims 2-4 that depend from claim 1, obviousness.

In Section IX (B) that is directed to overcoming the anticipation rejection based on DeLisi and in previous Section IX(C) that is directed to overcoming the obviousness rejection based on DeLisi in view of Hatada, Appellants have demonstrated that DeLisi does not teach, suggest, or in any way contemplate the features of the present invention that are to use free energy estimates that may be higher than a lowest free energy estimate possible for the molecule or the second generation molecules as specified according to the present invention.[2] The Hatada reference when added to DeLisi does not cure this infirmity. As such, DeLisi in view of Hatada does not render claim 1, or claims 2-4 that depend from claim 1, obvious. Thus, Appellants respectfully request that this rejection be withdrawn.

X. CONCLUSION

In the foregoing, Appellants have clearly traversed each of the Examiner's bases for rejecting amended claims 1-4 under 35 U.S.C. § 112, 1st paragraph, for allegedly not being enabling for de novo design of molecules that interact with any receptor; 35 U.S.C. § 102 for

[2] See the Appeal brief at Section IX(B), page 6, third paragraph, and Section IX(C), page 7, fourth paragraph.

allegedly being anticipated by DeLisi; 35 U.S.C. § 103 for allegedly being obvious in light DeLisi in view *Gulack*; and 35 U.S.C. § 103 for allegedly obvious in light of DeLisi in view Hatada. Accordingly Appellants request that the Board reverse the outstanding rejections and remand the application to Examiner and direct that the application be sent to issue.

No fees are believed due; however, please charge any additional fees due or overpayments to Deposit Account No. 08-0219.

Respectfully submitted,

Dated: May 3, 2005

Wayne M. Kennard
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CLAIMS

1. (Previously Amended) A method of de novo designing molecules that bind to a receptor site on a protein comprising the steps of:

(a) building a molecule in the receptor site comprising: adding successive random molecular fragments to an initial molecular fragment that is loaded into the receptor site, estimating the free energy of the molecule being grown after each addition of a molecular fragment, and orienting each successive molecular fragment as it is added to the receptor site such that the free energy estimate for the molecule may be higher than a lowest free energy estimate possible for the molecule;

(b) repeating step (a) to generate a collection of molecules grown in the receptor site, and ranking the collection of molecules according to increasing free energy estimates to identify high-ranking molecules;

(c) selecting one or more functional groups of a high-ranking molecule identified in step (b) as a single restart fragment and using the restart fragment to build a second-generation of molecules according to steps (a) and (b);

(d) minimizing the energy of a protein/ligand complex comprising the receptor site and a second-generation molecule using an empirical force field;

(e) quantitatively measuring the empirical interaction energy of the second-generation molecules, and ranking the second-generation molecules, wherein a second-generation molecule of low interaction strength is ranked higher than a second-generation molecule of more negative interaction energy is ranked higher than a second-generation molecule of less negative or positive interaction energy;

(f) modifying high-ranking second-generation molecules from step (e) based on qualitative analysis of the second-generation molecules including determination of chemical viability, synthetic feasibility, solubility, and effect of the second-generation molecule on the structure of the protein, whereas such modification comprises: atomic and/or functional substitutions, initiating growth from a specific receptor site, inclusion of salt bridges or hydrogen bonds, and solubility-enhancing measures;

(g) repeating steps (c) through (f) until a second-generation molecule is built which is identified as high-ranking in both steps (e) and (f); and

(h) displaying at least one second-generation molecule built according to step (g).

2. (Original) The method of claim 1, wherein the receptor site is selected from the group consisting of: Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, and human carbonic anhydrase II protein.

3. (Original) The method of claim 1, wherein the empirical interaction energy comprises CHARMM interaction energy.

4. (Original) The method of claim 1, wherein the empirical force field comprises CHARMM.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,584	06/29/2001	Robert S. DeWitte	426.97.265	3885

23483 7590 05/12/2003

HALE AND DORR, LLP
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EXAMINER	
LY, CHEYNE D	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 05/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 07-01)

HALE & DORR DOCKETING
RE: 42697.265US3
Action Date: 8.12.03
Action to be Taken: 2/0
Docketed By: LMB On: 5.15.03

Office Action Summary	Application No. 09/897,584	Applicant(s) DEWITTE ET AL.
	Examiner Cheyne D Ly	Art Unit 1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-4 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-4 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traversal of Group I, claims 1-4, in Paper No.8, filed March 04, 2003, is acknowledged.

2. It is acknowledged that claims 5-20 have been cancelled; therefore, Applicant's traversal of the restriction requirement is moot.

3. The requirement is still deemed proper and is therefore made FINAL.

4. Claims 1-4 are examined on the merits.

Priority

5. In order for the present application to receive benefit of priority for an invention to an earlier application, the earlier application (parent or provisional) must disclose the invention so as to be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112 regarding said invention. See Transco Products, Inc. v. Performance Contracting, Inc., 38 F.3d 551, 32 USPQ 2d 1077 (Fed. Cir. 1994). The specific claimed subject matter of the present application was not disclosed in the priority document (Application Number 08/741,866). Therefore, domestic priority under 35 U.S.C. §§ 120 and/or 121 has not been granted for the presently claimed subject matter.

Specification

6. The title of the invention is not descriptive. The title is objected to because the title is directed to a system and method for structure-based design that includes accurate prediction of binding free energy, however, the claims are directed to a method of de novo designing molecules that bind to a receptor site on a protein. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-4 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory algorithm type subject matter.

9. It is acknowledged that the claim subject matter is a method of de novo designing molecules based on free energy. However, claims 1-4 are rejected because they are directed to a non-statutory subject matter due to lacking any physical steps such as displaying the molecule, which has been designed. Currently, the steps are merely algorithmic processes of manipulating data directed to a molecule with its receptor without providing a means of visualizing the results of the said processes; therefore, the claim subject matter lacks a real world value. The critical steps of displaying the designed molecule would cause the subject matter in its entirety to be a practical application.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Specific to claim 1, steps (b) and (e), different types of ranking are cited in steps (b) and (e), however, it is unclear as to what is meant in step (e) as to whether the ranking of step(b) is utuilized or not. Clarification of the metes and bounds is required.

13. Claim 1 is regarded as indefinite because the method of the preamble differs from the active steps in the claim. The active steps of the claim support a method of building a molecule. However, the active steps of each claim do not accomplish the intended goal of the method, which is to design molecules de novo. Which component, the preamble or the active steps, of the claim control the metes and bounds of the claim? Currently, it is inconclusive as to which component is controlling the claims or how one is to design molecules de novo.

14. Claims 2-4 are rejected for the same reasons as for claim 1 due to being dependent from claim 1.

LACK OF ENABLEMENT UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for de novo design of molecules that interact with receptor sites of Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, or human carbonic anhydrase II protein, does not reasonably provide enablement for de novo design of molecules that interact with any receptor. Further, the instant specification is not enabling for the de novo design of any molecule to interact with any receptor site. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

17. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

18. Applicant discloses information present in crystal structures of proteins and crystal structures of protein-ligand may be used for predicting binding free energy which is necessary for the method of the claimed invention (Page 22, lines 19-22 to page 23, lines 1-4). It is acknowledged that the applicants have disclosed information to enable one skilled in the art to calculate the binding free energy for the molecules that interact with receptor sites of Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, or human carbonic anhydrase II protein (Example 2, pages 56-79).

19. However, it is well documented that protein crystallization is in essence a trial-and-error method, and the results are usually unpredictable (Drenth, J.). Further, as recently as November 1, 2002, Science published a New Focus article depicting the current state of the art for protein

crystallization that supports the unpredictability of the art. In essences, protein crystallization is still a trial and error process because the current technology for producing protein for the crystallization process is unpredictable, which results in high failure rate for proteins that are being crystallized. Therefore, researchers continue to have trouble generating sufficient protein required for the crystallization process (New Focus, Science, 2002). In light of the difficulty of the protein crystallization process, it is, therefore, unreasonable to expect one skilled in the art to use the method that relies on data that was derived from an unpredictable process such as protein crystallization for de novo molecule design of that interacts with any receptor site without undue experimentation.

Claim Rejections - 35 USC § 102

20. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

21. Claims 1, 3, and 4 are rejected under 35 U.S.C. 102(b) as being clearly by anticipated by DeLisi et al. (US 5,495,423 A).

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

22. Delisi et al. discloses a method of drug design. The factors that contribute to the said design process are surface complementary, ...electrostatic interaction energy, and solvation free energy (column 1, lines 39-44). In designing a peptide to bind to a receptor site, a peptide is docked to the receptor, each amino acid is placed in various orientations at each grid point, calculate the electrostatic interaction energy, those low-energy positions are selected, rank the

positions according to the minimized energies, the backbone between the terminal anchor residues is filled in, and the peptide is manufactured (Column 5, lines 22-65 to column 6, lines 3-27), as in claim 1, steps (a)-(c). The minimum energy locations for the charged end-residue is determined using a multi-copy mean-field energy minimization algorithm. A multi-copy mean-field approximation algorithm has been written as a modification of the software CHARMm Molecular modeling is performed with software ECEPP (Empirical Conformational Energy Program for Peptides, from Indiana University) (Column 10, lines 66-67 to column 11, lines 1-15), as in claims 1, step (d)-(g), 3 and 4.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

24. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

25. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeLisi et al. (US 5,495,423 A) in view of In re Gulack, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983).

26. DeLisi et al. discloses the limitations directed toward claim 1 as cited above. Even though the method disclosed by Delisi et al. does not specify that the receptor site is a Src-homolgy-2 domain, the specific limitations of Src-homolgy-2 (SH2) domain in this instant case do not distinguish the invention from the prior art in term of patentability because they are descriptive nonfunctional subject matter.

27. In re Gulack defines nonfunctional descriptive material, as when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in term of patentability. Also, the MPEP indicates that descriptive material that cannot exhibit any functional interrelationship with the way in which computing processes are performed does not constitute a statutory process, machine, manufacture or composition (MPEP § 2106 (IV)(B)(b)). Specific to the instant case, the method of de novo designing molecules merely process the data directed toward the Src-homolgy-2 domain without creating any functional interrelationship, either as part of the stored data or as part active steps of the said method, then such descriptive material alone does not impart functionality either to the data as so structured, or to the computer.

28. Clearly, a skilled artisan would have been motivated to partake the concept emphasized by DeLisi et al. for designing de novo molecules based on free energy. Further, the specific limitation of a SH2 domain is regarded as nonfunctional descriptive material as defined by In re Gulack. Therefore, it would have been obvious to one having ordinary skill in the art at the time

of the invention was made to use the crystal structure data for the SH2 domain in the method of DeLisi et al. for designing de novo molecules based on free energy.

29. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeLisi et al. (US 5,495,423 A) in view Hatada et al. (US 6251620 B1).

30. DeLisi et al. discloses the limitations directed toward claim 1 as cited above.

31. However, Delisi et al. does not specify that the receptor site is a Src-homolgy-2 domain.

32. Hatada et al. discloses that the three-dimensional structures of SH2 domain protein have been determined by X-ray crystallography (Abstract).

33. Clearly, a skilled artisan would have been motivated to partake the concept emphasized by DeLisi et al. for designing de novo molecules based on free energy (column 1, lines 39-44) and ligand and receptor interactions (column 1, lines 16-19); and improve on the said method by using the X-ray crystal coordinates of SH2 disclosed by Hatada et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the crystal structure data for the SH2 domain in the method of DeLisi et al. for designing de novo molecules based on free energy.

CONCLUSION

34. NO CLAIM IS ALLOWED.

35. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 193), and 1157

OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (703) 308-3880. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

37. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

38. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

C. Dune Ly
5/8/03

ARDIN H. MARSCHEL
PRIMARY EXAMINER

Subt. Form PTO-1449

INFORMATION DISCLOSURE IN AN APPLICATION

(Use several sheets if necessary)

Docket Number	Application Number
42697.265CON	09/897,584

Applicant	
DeWitte, et al.	

Sheet	1	OF	1

Filing Date	Group Art Unit
June 29, 2001	~~1651~~ 1631

#6

OIPE JC54 DEC 07 2001 PATENT & TRADEMARK OFFICE

U.S. Patent Documents

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

Foreign Patent Documents

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
cor	95/06293	3/2/95	WO				

Other Documents (Including Author, Title, Date Pertinent Pages, Etc.)

cor	A1	Abdel-Meguid, S. S., et al. "An Orally Bioavailable HIV-1 Protease Inhibitor Containing an Imidazole-Derived Peptide Bond Replacement: Crystallographic and Pharmacokinetic " *Biochemistry*, Vol. 33, No. 9, pp. 11671-11677 (1994)
	A2	Thompson, S. K., et al., "Rational Design, Synthesis, and Crystallographic Analysis of a Hydroxyethylene-Based HIV-1 Protease Inhibitor Containing a Heterocyclic P1-P2 Amide Bond Isostere" *J. Med. Chem.*, Vol. 37, pp. 3100-3107 (1994)
	A3	Botter, Angelika, et al., "Design of a Synthetic Mdm2-binding Mini Protein That Activates the p53 Response in vivo" *Curr Biol.*, Vol. 7, No. 11, pp. 860-869 (1997)
	A4	Sigal and Whitesides, " Benzenesulfonamide-Peptide Conjugates As Probes For Secondary Binding Sites Near The Active Site of Carbonic Anhydrase" *Bioorganic and Med. Chem. Ltrs*, Vol. 6, No. 5, pp. 559-564 (1996)

EXAMINER	DATE CONSIDERED
	4/23/03

EXAMINER: Initial if citation is considered, whether or not citation is in conformance with MPEP § 609: Draw Line through citation if not conformance and not considered. Include copy with next communication to applicant.

Subt. Form PTO-1449	Docket Number	Application Number
INFORMATION DISCLOSURE IN AN APPLICATION *(Use several sheets if necessary)*	42697.265CON	09/897,584
	Applicant: DeWitte, et al.	
Sheet 1 OF 1	Filing Date: June 29, 2001	Group Art Unit: ~~1654~~ 1631

#6

OIPE JC54 DEC 07 2001 PATENT & TRADEMARK OFFICE

U.S. Patent Documents

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

Foreign Patent Documents

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
CM	95/06293	3/2/95	WO				

Other Documents (Including Author, Title, Date Pertinent Pages, Etc.)

CM	A1	Abdel-Meguid, S. S., et al. "An Orally Bioavailable HIV-1 Protease Inhibitor Containing an Imidazole-Derived Peptide Bond Replacement: Crystallographic and Pharmacokinetic " *Biochemistry*, Vol. 33, No. 9, pp. 11671-11677 (1994)
	A2	Thompson, S. K., et al., "Rational Design, Synthesis, and Crystallographic Analysis of a Hydroxyethylene-Based HIV-1 Protease Inhibitor Containing a Heterocyclic P1-P2 Amide Bond Isostere" *J. Med. Chem.*, Vol. 37, pp. 3100-3107 (1994)
	A3	Botter, Angelika, et al., "Design of a Synthetic Mdm2-binding Mini Protein That Activates the p53 Response in vivo" *Curr Biol.*, Vol. 7, No. 11, pp. 860-869 (1997)
	A4	Sigal and Whitesides, " Benzenesulfonamide-Peptide Conjugates As Probes For Secondary Binding Sites Near The Active Site of Carbonic Anhydrase" *Bioorganic and Med. Chem. Ltrs*, Vol. 6, No. 5, pp. 559-564 (1996)

EXAMINER	DATE CONSIDERED
	4/23/03

EXAMINER: Initial if citation is considered, whether or not citation is in conformance with MPEP § 609: Draw Line through citation if not conformance and not considered. Include copy with next communication to applicant.

Notice of References Cited	Application/Control No. 09/897,584	Applicant(s)/Patent Under Reexamination DEWITTE ET AL.	
	Examiner Cheyne D Ly	Art Unit 1631	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-5,495,423	02-1996	DeLisi et al.	703/2
	B	US-6,251,620 B1	06-2001	Hatada et al.	435/15
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

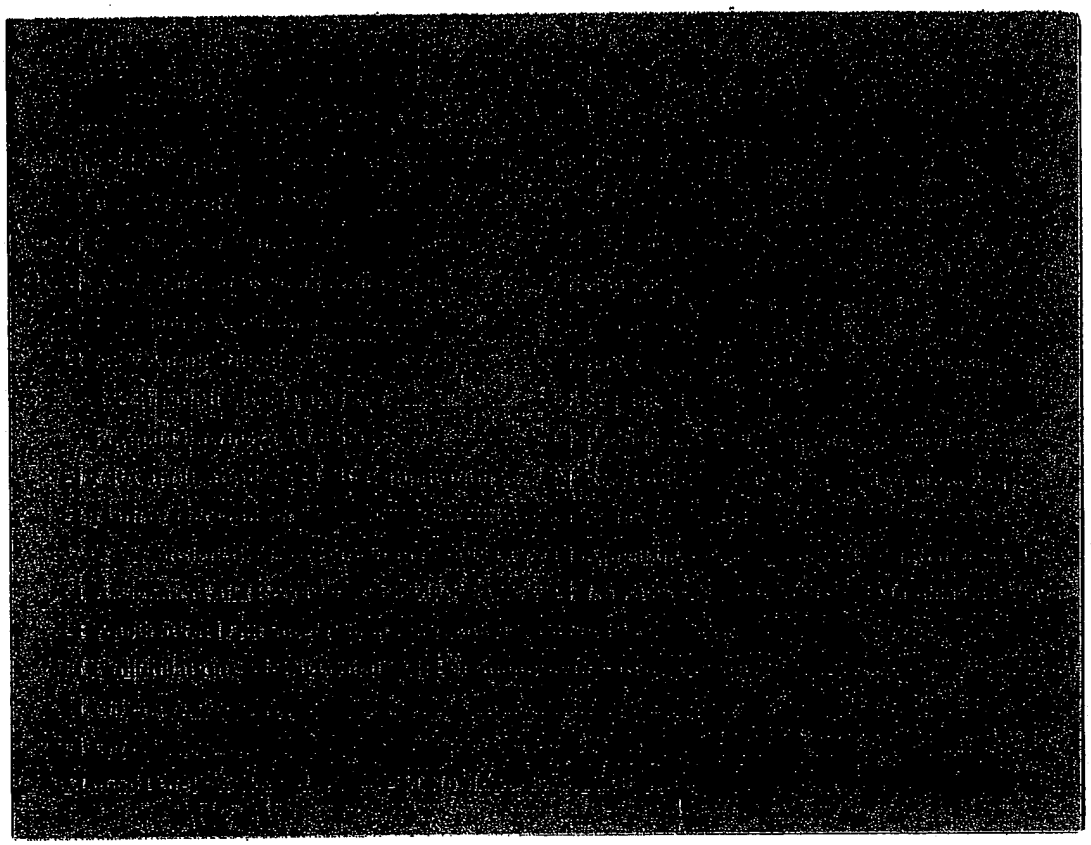
FOREIGN PATENT DOCUMENTS

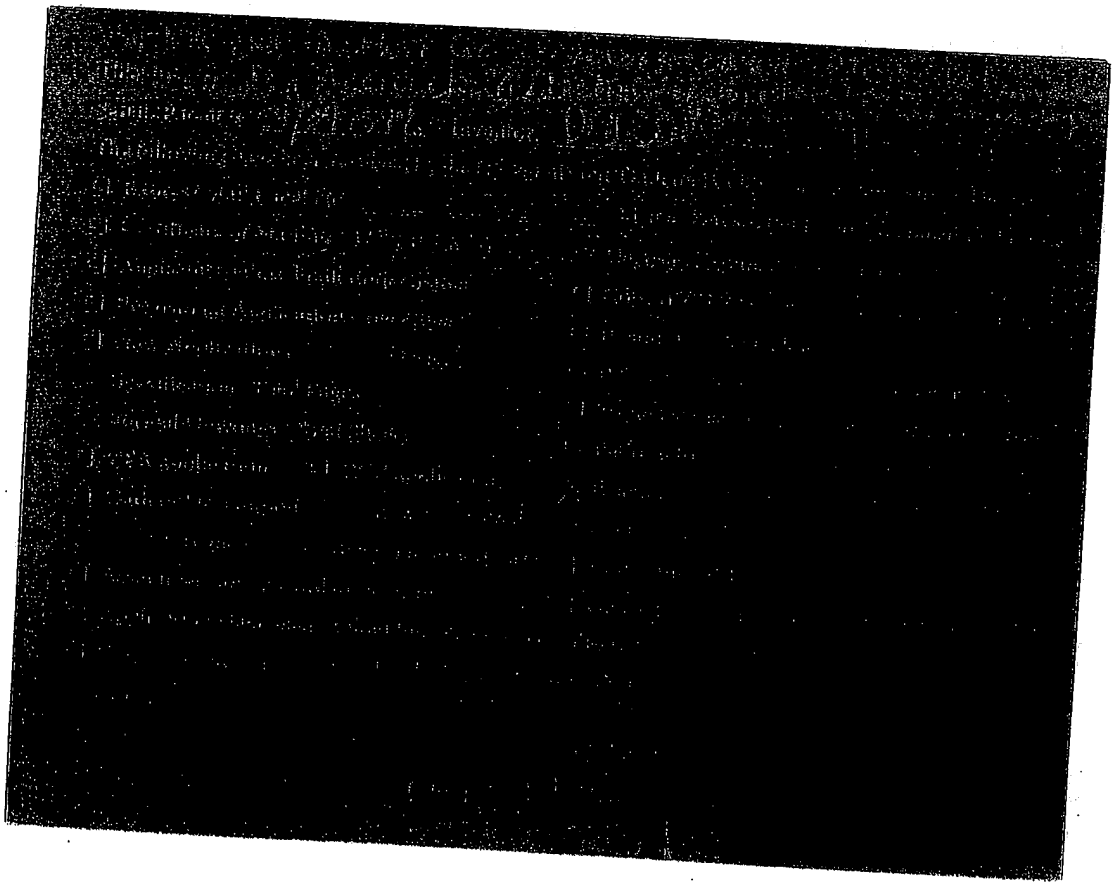
*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	News Focus, Science, November 1, 2002, Volume 298, Pages 948-950.
	V	Jan Drenth, Principles of Protein X-ray Crystallography, 1995, Springer-Verlag, page 16.
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.





PTO/SB/21 (05-03)
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/625,125
Filing Date	06/28/2003
First Named Inventor	Robert S. DeWitte
Art Unit	1631
Examiner Name	Chunyuan Liu
Attorney Docket Number	4262.2650cip
Total Number of Pages in This Submission	

ENCLOSURES (Check all that apply)

- [ ] Fee Transmittal Form
- [ ] Fee Attached
- [x] Amendment/Reply
- [ ] After Final
- [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
- [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [x] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] After Allowance communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group (Appeal Notice, Brief, Reply Brief)
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please identify below):
  - Postcard

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Wayne M. Kennard
Signature	
Date	08/06/2003

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Typed or printed name	Susie Fernandez		
Signature		Date	08/06/2003

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s):	Robert S. DeWitte et al.
Serial No.:	09/897,584
Filed:	June 29, 2001
Title:	System and Method for Structure-Based Design That Includes Accurate Prediction of Binding Free Energy
Examiner:	Cheyne Ly
Unit:	1631

Mail Stop Non-Fee Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY

Sir:

This is a response to the Office Action dated May 12, 2003. Applicants have considered the Examiner's remarks in the Office Action and amended the application to place it in condition for allowance. Accordingly, the application has been amended as follows:

IN THE SPECIFICATION

Page 1, delete the title at lines 1-2 and insert:

--A Method for De Novo Designing Molecules for Binding to Receptor Sites"--

Page 1, delete lines 3 and 4 and insert the following:

-- Related Applications

This application is a continuation of U.S. Serial No. 09/220,363 filed December 24, 1998, now abandoned, which is a continuation-in-part of U.S. Serial No. 08/741,866 filed September 26, 1996, which is now U.S. Patent No. 5,854,992.--

Page 91, delete the title at lines 1-4 and insert:

--A Method for De Novo Designing Molecules for Binding to Receptor Sites"--

IN THE CLAIMS

1. (Currently Amended) A method of de novo designing molecules that bind to a receptor site on a protein comprising the steps of:

(a) building a molecule in the receptor site comprising: adding successive random molecular fragments to an initial molecular fragment that is loaded into the receptor site, estimating the free energy of the molecule being grown after each addition of a molecular fragment, and orienting each successive molecular fragment as it is added to the receptor site such that the free energy estimate for the molecule may be higher than a lowest free energy estimate possible for the molecule;

(b) repeating step (a) to generate a collection of molecules grown in the receptor site, and ranking the collection of molecules according to increasing free energy estimates to identify high-ranking molecules;

(c) selecting one or more functional groups of a high-ranking molecule identified in step (b) as a single restart fragment and using the restart fragment to build a second-generation of molecules according to steps (a) and (b);

(d) minimizing the energy of a protein/ligand complex comprising the receptor site and a second-generation molecule using an empirical force field;

(e) quantitatively measuring the empirical interaction energy of the second-generation molecules, and ranking the second-generation molecules, wherein a second-generation molecule of low interaction strength is ranked higher than a second-generation molecule of more negative interaction energy is ranked higher than a second-generation molecule of less negative or positive interaction energy;

(f) modifying high-ranking second-generation molecules from step (e) based on qualitative analysis of the second-generation molecules including determination of chemical viability, synthetic feasibility, solubility, and effect of the second-generation molecule on the structure of the protein, whereas such modification comprises: atomic and/or functional substitutions, initiating growth from a specific receptor site, inclusion of salt bridges or hydrogen bonds, and solubility-enhancing measures[.];

(g) repeating steps (c) through (f) until a second-generation molecule is built which is identified as high-ranking in both steps (e) and (f)[.]; and

(h) displaying at least one second-generation molecule built according to step (g).

2. (Original) The method of claim 1, wherein the receptor site is selected from the group consisting of: Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, and human carbonic anhydrase II protein.

3. (Original) The method of claim 1, wherein the empirical interaction energy comprises CHARMM interaction energy.

4. (Original) The method of claim 1, wherein the empirical force field comprises CHARMM.

5. (Cancelled).

6. (Cancelled).

7. (Cancelled).

8. (Cancelled).

9. (Cancelled).

10. (Cancelled).

11. (Cancelled).

12. (Cancelled).

13. (Cancelled).

14. (Cancelled).

15. (Cancelled).

16. (Cancelled).

17. (Cancelled).

18. (Cancelled).

19. (Cancelled).

20. (Cancelled).

Remarks

Claims 1-4 are currently pending in the present application. Applicants acknowledge the Examiner's acceptance of the election of the claims 1-4 to prosecute in the present application.

In the Office Action dated May 12, 2003, the Examiner objected to the specification of certain grounds and rejected claims 1-4 on other grounds. Applicants will address and traverse each of the Examiner's grounds for objection and rejection in this Reply, thereby placing the present application in condition for allowance.

I. Priority

In numbered paragraph 5 of the Office Action, the Examiner indicated that priority to the earlier filed application U.S. Serial No. 08/741,866 would not be granted because the claimed subject matter of the present invention is not disclosed in that application. Applicants submit that this action of the Examiner is improper and Applicants should be granted priority based on the earlier application.

The present application is a continuation of U.S. Serial No. 09/220,363 filed December 24, 1998, now abandoned, which is a continuation-in-part of U.S. Serial No. 08/741,866 filed September 26, 1996, which is now U.S. Patent No. 5,854,992. This information about the present application is confirmed by the Official Filing Receipt attached as Attachment 1 to this Reply.

The specification of the present invention is the same as the specification of U.S. Serial No. 09/220,363. This specification supports pending claims 1-4 of the present invention. This specification of U.S. Serial No. 09/220,363 and the present application contain additional subject matter compared to U.S. Serial No. 08/741,866, thus U.S. Serial No. 09/220,363 was filed as a continuation-in-part application. Since the present application is a continuation of U.S. Serial No. 09/220,363 not 08/741,866, the Examiner should grant priority as specified in the Official Filing Receipt and withdraw this rejection.

II. Specification

In numbered paragraph 6 of the Office Action, the Examiner objected to the title as being non-descriptive on the claimed invention. Applicants have reviewed the pending claims on the application and have amended the title as appropriate to overcome this objection. As such, this objection should be withdrawn.

III. Claims 1-4 Define Statutory Subject Matter

At paragraphs 7-9, the Examiner rejected claims 1-4 under 35 U.S.C. §101 for being directed to allegedly non-statutory subject matter. The Examiner suggested that a way to overcome this rejection was to add a "displaying step" to independent claim 1. Although Applicants do not agree that the claims 1-4 only define an algorithm, they have amended the claim 1 to include a displaying step as suggested by the Examiner. Thus, Applicants have overcome the Examiner's §101 rejection and request that it be withdrawn.

IV. Claims 1-4 are Definite

At paragraphs 10-14, the Examiner has rejected claims 1-4 for being indefinite under 35 U.S.C. § 112, second paragraph. The Examiner has two contentions that allegedly support this rejection. The first is that Steps (b) and (e) of claim 1 recite different types of rankings, and the second is that allegedly the preamble differs from the active steps of claim 1. As will be shown, each of these bases for rejection is traversed.

The Examiner's first basis for rejection is that the rankings are different at Steps (b) and (e), and clarification is requested. At Step (b), a collection of molecules grown according Step (a) are ranked based on their individual free energy estimates so that the high-ranking molecules with the lowest estimated free energy may be identified. The ranking at Step (e) is based on the actions at Steps (c) and (d). At Step (c), one or more of the functional groups from the high-ranking molecules identified at Step (b) is used as the start fragment for the growth of a set of second-generation molecules. The ranking that is taking place at Step (e) is of these second-generation molecules.

To overcome the Examiner's first basis for rejection under 35 U.S.C. § 112, second paragraph, claim 1 has been clarified to show the difference in what is ranked at

Steps (b) and (e). Therefore, Applicants request that this basis for rejection for indefiniteness be withdrawn.

The Examiner's second basis for rejecting claims 1-4 for indefiniteness is that the active steps of claim 1 differ from the preamble. Applicants are confused by the Examiner's comments associated with this basis for rejection. The preamble of claim 1 recites that the claim is directed to "de novo" molecular design for a receptor site. This is exactly what takes place at the receptor site according to the active steps of claim 1 and claims 2-4 that depend from claim 1. More specifically, the de novo drug design of claims 1-4 is directed to the development of molecules that are appropriate to bind specific receptor sites. This is accomplished in two phases: (1) Steps (a) and (b); and (2) Steps (c) to (h). There is no incongruity between the preamble and active steps of claims 1-4. Thus, this basis of rejection under § 112, second paragraph is overcome as Applicants understand the rejection. Accordingly, this basis of rejection is overcome and should be withdrawn.

V. Claims 1-4 are Enabling

At numbered paragraphs 15-19, the Examiner has rejected claims 1-4 for being non-enabling. The Examiner's main thrust is that claim 1-4 are enabling for the receptor sites recited in claim 2 but not generally for any receptor site. More specifically, the Examiner is contending that the scope of claims 1-4 should be limited to only the receptor sites recited in claim 2. Applicants submit that this is an undue limitation being suggested by the Examiner.

The specification at page 17, lines 11-14, indicates that in "one embodiment" a receptor site could be selected from the ones set forth in claim 2. Moreover, at page 59, lines 7-10, it states that the receptor sites set forth in claims 2 are preferred, not the only receptor sites for which the present invention is useful. The language that is set forth at these locations of the specification does not indicate in any way that these are the only receptor sites that may be used with the present invention. The receptor sites that are recited at these places in the specification and claimed at claim 2 are to satisfy the best mode requirements of § 112 and not an ultimate limitation for claims 1-4.

If there are receptor sites besides the ones that are recited in claim 2, the process that is set forth in claim 1 still may be used without undue experimentation to build appropriate molecules. The person choosing such a different receptor site would use exactly the same process for the collection and ranking of molecules at Steps (a) and (b), then that person would develop the second-generation molecules according to Steps (c) to (h). Thus, one skilled in the art would know how to make and use the present invention without undue experimentation. Moreover, the Examiner has not indicated anywhere in the specification that would support the contention that claims 1-4 should be limited to only the receptor sites recited in claim 2. Accordingly, Applicants have demonstrated that claims 1-4 should not be limited to only the receptor suites recited in claim 2, but could be used with other receptor sites without undue experimentation and still be within the scope of the present invention.

The Examiner in numbered paragraph 19 contends that protein crystallization is a trial and error method, and unpredictable, and, as such, claims 1-4 are not enabling. Applicants submit that the Examiner may be misunderstanding the present invention.

The section of the specification to which the Examiner points to support that method of the present invention is non-enabling is page 22, line 19 to page 23, line 4. However, the entire section that includes the partial section cited by the Examiner states the following (Page 22, line 16 to Page 23, line 4):

> The course-graining model with knowledge-based potential data follows from the application of the principles of canonical statistical mechanics to subsets of proteins. In particular, the model includes the determination that small subsets of a folded protein are in thermal equilibrium with each other. As such, the present invention employs these principles. Thus, there is a reasonable basis to contend that the information present in the crystalline structures of proteins and crystal structures of protein-ligand complexes may be disassembled into constituent parts and the contribution of each part to the binding free energy may be assigned on the basis of probability. This permits the present invention to achieve the more accurate results for binding free energy predictions and applying them in the building of molecules or ligands. [Emphasis added.]

Even in light of the Examiner's statements to the contrary, a person skilled in the art would understand the contributions of the parts of the crystalline structure to binding free energy. The Examiner is to be reminded that according to the present invention these

contributions are to be handled as values that are assigned based on probability. Thus, a person of ordinary skill in the art could carry out these assignments without undue experimentation. The contribution being referred to at this portion of the process is not the principal determination the binding free energy, as the Examiner infers, but, as stated, is to assist in making more accurate predictions which are within the capabilities of a person of ordinary skill in the art without undue experimentation.

Applicants, therefore, have traversed the Examiner's bases for rejection claims 1-4 under 35 U.S.C. § 112, first paragraph, and request that it be withdrawn.

VI. Claims 1-4 are not Anticipated by DeLisi

The Examiner at numbered paragraphs 20-22 rejected claims 1-4 under 35 U.S.C. § 102 for anticipation based on U.S. Patent No. 5,495,423 to DeLisi et al. ("DeLisi"). Applicants submit that pending claims 1-4 are not anticipated by DeLisi.

Claim 1, as amended, recites a method that includes Steps (a) and (b) that are directed to the first selection and ranking of molecules, and Steps (c)-(h) directed to the second-generation molecules that are derived from one or more functional groups of the high-ranking molecules determined at Steps (a) and (b). The DeLisi patent does not disclose or suggest in any way the method of claim 1 that builds a first collection of molecules and then builds second-generation molecules from one or more functional groups of the high-ranking molecules of the first collection. Therefore, DeLisi does not teach or suggest each and every element of claim 1 in the same way as is necessary for DeLisi to anticipate claim 1 of the present application under § 102.

Claims 2-4 depend from claim 1, and, as such, each contain all of the features of claims 1. Since DeLisi does not anticipate claim 1 as demonstrated above, claims 2-4 are not anticipated for the same reasons.

Noting the foregoing, Applicants have traversed the Examiner's anticipation rejection. Thus, Applicants request that this rejection be withdrawn.

VII. Claims 1-4 are not Obvious

At numbered paragraphs 23-28, the Examiner has rejected claims 1-4 under 35 U.S.C. § 103 for obviousness based on U.S. Patent No. 5,495,423 to DeLisi et al. ("DeLisi") in view of *In re Gulack*, 703 F. 2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir.

1983). The Examiner in rejecting claims 1-4 for obviousness contends that "DeLisi et al. discloses the limitations directed toward claim 1..." and *In re Gulack* defines what is nonfunctional descriptive material and when such descriptive material will not distinguish the invention from the prior art in terms of patentability. Applicant submits that the references of this combination taken alone or in combination do not render obvious the invention of claims 1-4 of the present application

As set forth in Section VI above, DeLisi does not teach or suggest the invention of claims 1-4. For these same reasons, DeLisi alone clearly does not render claims 1-4 obvious. The Federal Circuit case *In re Gulack* that the Examiner cited to combine with DeLisi does not in any way overcome the deficiencies in DeLisi to provide a basis for rendering claims 1-4 obvious. Therefore, claims 1-4 are not obvious in light of DeLisi in view of *In re Gulack*, and Applicants request that this obviousness rejection be withdrawn.

The Examiner has also rejected claims 1-4 for obviousness based on DeLisi in view of U.S. Patent No. 6,251,620 B1 to Hatada et al. ("Hatada"). In this combination, DeLisi is cited for disclosing all of the limitations of claim 1 and Hatada is cited for disclosing that three-dimensional structures of SH2 domain proteins have been determined by X-ray crystallography. Applicants submit that claims 1-4 are not rendered obvious by this combination.

As set forth in Section VI above, DeLisi does not teach or suggest the invention of claims 1-4. For these same reasons, DeLisi alone clearly does not render claims 1-4 obvious. Hatada does not in any way overcome the deficiencies in DeLisi to provide a basis for rendering claims 1-4 obvious when it is added to DeLisi. As such, claims 1-4 are not obvious in light of DeLisi in view of Hatada, and Applicants request that this obviousness rejection be withdrawn.

Conclusion

Claims 1-4 are pending in the present application. Applicants have traversed each of the Examiner's bases for objecting to the specification or rejecting the claims, thereby placing the present application in condition for allowance.

The present invention is new, non-obvious and useful. Given that Applicants have traversed each and every objection or rejection raised by the Examiner in the Office Action dated May 12, 2003, the application is in condition for allowance and it is requested that it be passed to issue in due course.

In the event a fee is due, the Commissioner is authorized to charge any required fee to maintain the pendency of this application, or to credit any overpayment to Deposit Account No. 08-0219.

Respectfully submitted,

Dated: August 6, 2003

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Attachment 1

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APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
09/897,584	06/29/2001	1651	780	426.97.265	16	20	8

HALE AND DORR LLP
SEP 27 2001
INTELLECTUAL PROPERTY DEPARTMENT

23483
HALE AND DORR, LLP
60 STATE STREET
BOSTON, MA 02109

CONFIRMATION NO. 3885
UPDATED FILING RECEIPT

OC000000006786612

Date Mailed: 09/25/2001

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Robert S. DeWitte, Gurnee, IL;
Eugene I. Shakhnovich, Lexington, MA;

Domestic Priority data as claimed by applicant

THIS APPLICATION IS A CON OF 09/220,363 12/24/1998 ABN
WHICH IS A CIP OF 08/741,866 09/26/1996 PAT 5,854,992

Foreign Applications

If Required, Foreign Filing License Granted 07/27/2001

Projected Publication Date: 01/03/2002

Non-Publication Request: No

Early Publication Request: No

**** SMALL ENTITY ****

Title

System and method for structure-based drug design that includes accurate prediction of binding free energy

Preliminary Class

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/897,584	06/29/2001	Robert S. DeWitte	426.97.265	3885

23483 7590 10/08/2003

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EXAMINER	
LY, CHEYNE D	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 10/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

HALE & DORR DOCKETING
RE: 42697.265 US3
Action Date: 1.8.04
Action to be Taken: D/O
Docketed By: BMB On: 10.12.03

PTO-90C (Rev. 10/03)

Office Action Summary	Application No. 09/897,584	Applicant(s) DEWITTE ET AL.	
	Examiner Cheyne D Ly	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicants' arguments filed August 08, 2003 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

2. The new title has been accepted.

3. Claims 1-4 are examined on the merits.

Priority

4. In order for the present application to receive benefit of priority for an invention to an earlier application, the earlier application (parent or provisional) must disclose the invention so as to be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112 regarding said invention. See Transco Products, Inc. v. Performance Contracting, Inc., 38 F.3d 551, 32 USPQ 2d 1077 (Fed. Cir. 1994). The specific claimed subject matter of the present application was not disclosed in the priority document (Application Number 08/741,866). Therefore, domestic priority under 35 U.S.C. §§ 120 and/or 121 has not been granted for the presently claimed subject matter.

1. It is noted that the instant application complies with the requirements of the first paragraph of 35 U.S.C. 112 regarding said invention as directed to U.S. Serial No. 09/220,363 filed December 24, 1998. Therefore, domestic priority under 35 U.S.C. §§ 120 and/or 121 has been granted for the presently claimed subject matter.

LACK OF ENABLEMENT UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for de novo design of molecules that interact with receptor sites of Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, or human carbonic anhydrase II protein, does not reasonably provide enablement for de novo design of molecules that interact with any receptor. Further, the instant specification is not enabling for the de novo design of any molecule to interact with any receptor site. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

7. This rejection is maintained with respect to claims 1-4 as recited in the previous office action mailed May 12, 2003.

Response to Applicant's argument

8. Applicant argues that the language set forth in the instant specification (page 17, lines 11-14 and 59, lines 7-10) does not limit the claimed invention wherein the scope enablement is limited to the de novo design of molecules that interact with receptor sites of Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, or human carbonic anhydrase II protein. Further, one of skill in the art would be able to practice the claimed invention without undue experimentation because one of skill in the art would understand the contributions of the parts of the crystalline structure to binding free energy. Applicant's argument has been fully considered and found to be unpersuasive due to the limiting

guidance provided via working examples for a method that relies on data (binding free energy) derived from a method directed to an unpredictable art, protein crystallization. Therefore, the instant application provide adequate guidance to one of skill in the art to practice said invention as directed to Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, or human carbonic anhydrase II protein; however, one of skill in the art would not be able practice said invention with any other protein without undue experimentation as discussed below.

9. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

10. Applicant discloses information present in crystal structures of proteins and crystal structures of protein-ligand may be used for predicting binding free energy which is necessary for the method of the claimed invention (Page 22, lines 19-22 to page 23, lines 1-4). It is acknowledged that the applicants have disclosed information to enable one skilled in

the art to calculate the binding free energy for the molecules that interact with receptor sites of Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, or human carbonic anhydrase II protein (Example 2, pages 56-79).

11. However, it is well documented that protein crystallization is in essence a trial-and-error method, and the results are usually unpredictable (Drenth, J.). Further, as recently as November 1, 2002, Science published a New Focus article depicting the current state of the art for protein crystallization that supports the unpredictability of the art. In essences, protein crystallization is still a trial and error process because the current technology for producing protein for the crystallization process is unpredictable, which results in high failure rate for proteins that are being crystallized. Therefore, researchers continue to have trouble generating sufficient protein required for the crystallization process (New Focus, Science, 2002). In light of the difficulty of the protein crystallization process, it is, therefore, unreasonable to expect one skilled in the art to use the method that relies on data that was derived from an unpredictable process such as protein crystallization for de novo molecule design of that interacts with any receptor site without undue experimentation.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

13. Claims 1, 3, and 4 are rejected under 35 U.S.C. 102(b) as being clearly by anticipated by DeLisi et al. (US 5,495,423 A).

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

14. This rejection is maintained with respect to claims 1, 3, and 4 as recited in the previous office action mailed May 12, 2003.

15. Applicant argues by amendment that Delisi et al. does not disclose the building of second-generation molecules from one or more functional groups of high-ranking molecules of the first collection. Applicant's argument has been found to be unpersuasive due to the disclosure wherein the method of Delisi et al. comprises retrieving previously established low-energy amino acid (highest ranking), selecting a ligand anchor pair from among the low-energy amino acid configurations (second-generation molecules) (column 3, lines 8-13).

16. It is re-iterated Delisi et al. discloses a method of drug design. The factors that contribute to the said design process are surface complementary, ...electrostatic interaction energy, and solvation free energy (column 1, lines 39-44). In designing a peptide to bind to a receptor site, a peptide is docked to the receptor, each amino acid is placed in various orientations at each grid point, calculate the electrostatic interaction energy, those low-energy positions are selected, rank the positions according to the minimized energies, the backbone between the terminal anchor residues is filled in, and the peptide is manufactured (Column 5, lines 22-65 to column 6, lines 3-27), as in claim 1, steps (a)-(c). The minimum energy locations for the charged end-residue is determined using a multi-copy mean-field energy minimization algorithm. A multi-copy mean-field approximation algorithm has been written as a modification of the software CHARMm Molecular modeling is performed with software ECEPP (Empirical Conformational Energy Program for Peptides, from Indiana University) (Column 10, lines 66-67 to column 11, lines 1-15), as in claims 1, step (d)-(g), 3 and 4.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeLisi et al. (US 5,495,423 A) in view of In re Gulack, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983).

20. This rejection is maintained with respect to claims 1-4 as recited in the previous office action mailed May 12, 2003.

21. Applicant argues by amendment that Delisi et al. does not disclose the building of second-generation molecules from one or more functional groups of high-ranking molecules of the first collection. Applicant's argument has been found to be unpersuasive as discussed above.

22. DeLisi et al. discloses the limitations directed toward claim 1 as cited above. Even though the method disclosed by Delisi et al. does not specify that the receptor site is a Src-homolgy-2 domain, the specific limitations of Src-homolgy-2 (SH2) domain in this instant case do not distinguish the invention from the prior art in term of patentability because they are descriptive nonfunctional subject matter.

23. In re Gulack defines nonfunctional descriptive material, as when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in term of patentability. Also, the MPEP indicates that descriptive material that cannot exhibit any functional interrelationship with the way in which computing processes are performed does not constitute a statutory process, machine, manufacture or composition (MPEP § 2106 (IV)(B)(b)). Specific to the instant case, the method of de novo designing molecules merely process the data directed toward the Src-homolgy-2 domain without creating any functional interrelationship, either as part of the stored data or as part active steps of the said method, then such descriptive material alone does not impart functionality either to the data as so structured, or to the computer.

24. Delisi et al. discloses an improvement for computing efficiency as directed to drug design strategies (column 1, lines 55 to column 2, lines 2) wherein data is derived from 3D molecular models (column 5, lines 55-65).

25. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated to partake the improvement suggested by DeLisi et al. for designing de novo molecules based on free energy. Further, the specific limitation of a SH2 domain is regarded as nonfunctional descriptive material as defined by In re Gulack. Therefore, it would have

been obvious to one having ordinary skill in the art at the time of the invention was made to use the crystal structure data for the SH2 domain in the method of DeLisi et al. for designing de novo molecules based on free energy.

26. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over DeLisi et al. (US 5,495,423 A) in view Hatada et al. (US 6251620 B1).

27. This rejection is maintained with respect to claims 1-4 as recited in the previous office action mailed May 12, 2003.

28. DeLisi et al. discloses the limitations directed toward claim 1 as cited above.

29. However, Delisi et al. does not specify that the receptor site is a Src-homolgy-2 domain.

30. Hatada et al. discloses that the three-dimensional structures of SH2 domain protein have been determined by X-ray crystallography (Abstract).

31. Delisi et al. discloses an improvement for computing efficiency as directed to drug design strategies (column 1, lines 55 to column 2, lines 2) wherein data is derived from 3D molecular models (column 5, lines 55-65).

32. An artisan of ordinary skill in the art at the time of the instant invention would have been motivated to partake the improvement suggested by DeLisi et al. for designing de novo molecules based on free energy; and improve on the said method by using the X-ray crystal coordinates of SH2 disclosed by Hatada et al. Therefore, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to use the crystal structure data for the SH2 domain as taught by Hatada et al. in the method of DeLisi et al. for designing de novo molecules based on free energy.

CONCLUSION

33. NO CLAIM IS ALLOWED.

34. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

35. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

36. Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 193), and 1157 OG 94 (December 28, 1993) (see 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242 or (703) 305-3014.

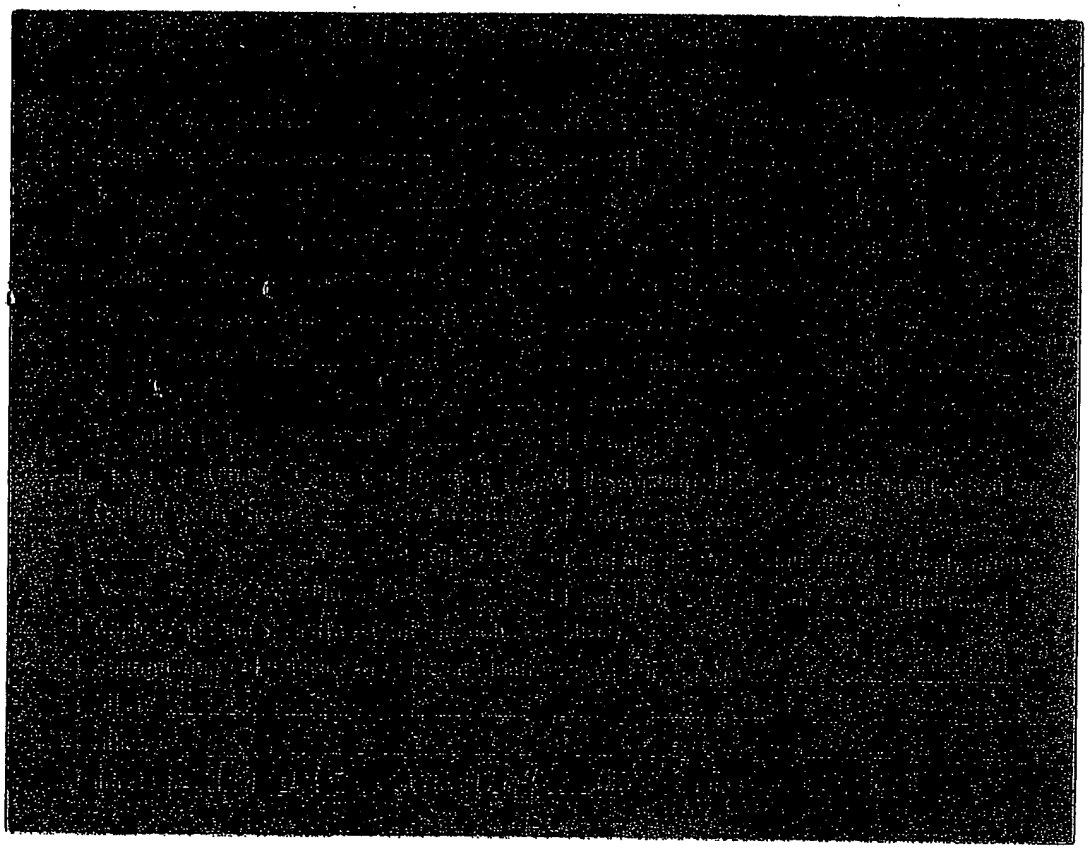
37. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (703) 308-3880. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

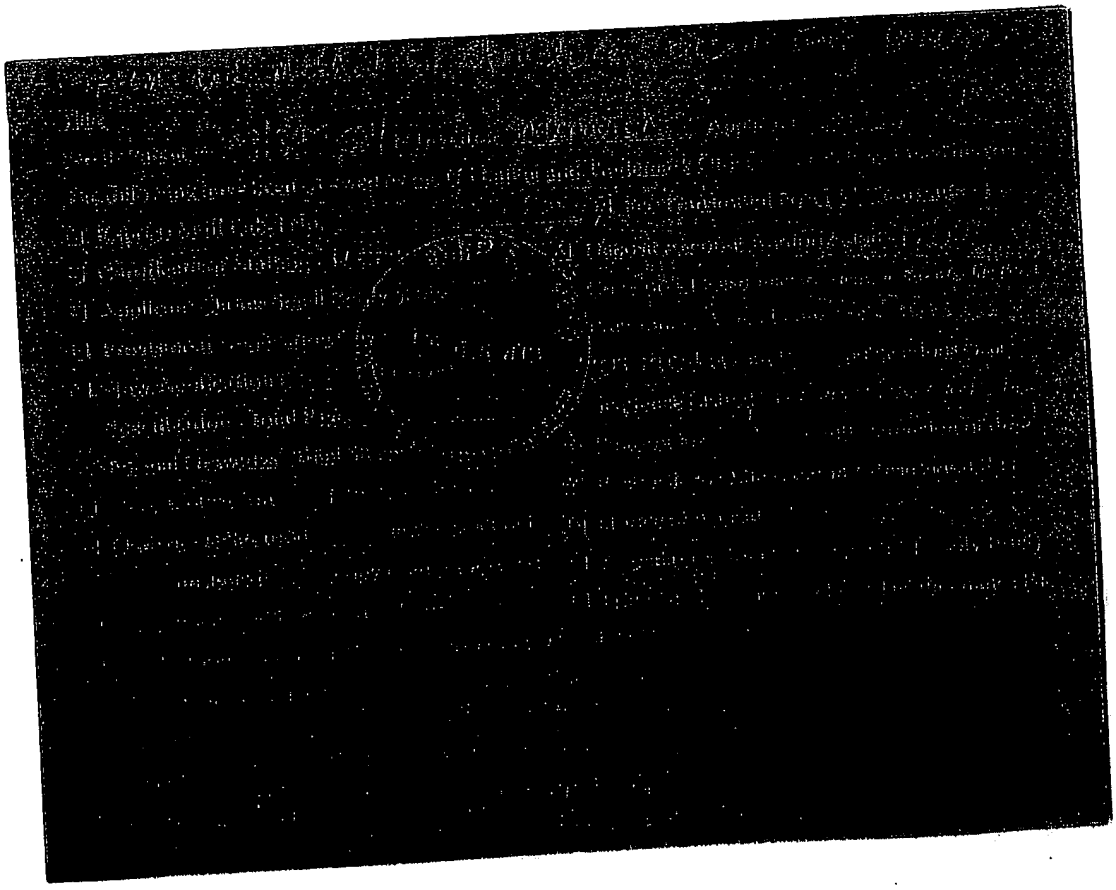
38. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028.

39. Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner, Tina Plunkett, whose telephone number is (703) 305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

C. Dune Ly
10/2/03

ARDIN H. MARSCHEL
PRIMARY EXAMINER





PTO/SB/21 (08-03)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	[illegible]
Filing Date	06/29/2001
First Named Inventor	Susumu Shakmori et al.
Art Unit	1623
Examiner Name	Chaynie Ly
Attorney Docket Number	2697.266

Total Number of Pages in This Submission: 6

ENCLOSURES (Check all that apply)

- [x] Fee Transmittal Form
- [ ] Fee Attached
- [x] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [x] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Response to Missing Parts/ Incomplete Application
  - [ ] Response to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
- [ ] After Allowance communication to Group
- [x] Appeal Communication to Board of Appeals and Interferences
- [ ] Appeal Communication to Group (Appeal Notice, Brief, Reply Brief)
- [ ] Proprietary Information
- [ ] Status Letter
- [x] Other Enclosure(s) (please identify below):
  - Postcard

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	Wayne M. Kennard
Signature	[signature]
Date	4-07-04

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

Typed or printed name	Susie Fernandez		
Signature	[signature]	Date	4-7-04

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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NOTICE OF APPEAL FROM THE EXAMINER TO THE BOARD OF PATENT APPEALS AND INTEFERENCES

Docket Number (Optional): 42697.265

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" on 4-7-04

Signature: Susie Fernandez

Typed or printed name: Susie Fernandez

In re Application of: Eugene Shaknovich et al.

Application Number	Filed
09/897,584	06/29/2001

For: System and Method for Structure-Based Drug

Art Unit	Examiner
1631	Cheyne Ly

Applicant hereby appeals to the Board of Patent Appeals and Interferences from the last decision of the examiner.

The fee for this Notice of Appeal is (37 CFR 1.17(b)) $ 330

- ☐ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee shown above is reduced by half, and the resulting fee is: $ _____
- ☑ A check in the amount of the fee is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director has already been authorized to charge fees in this application to a Deposit Account. I have enclosed a duplicate copy of this sheet.
- ☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. 08-0219 . I have enclosed a duplicate copy of this sheet.
- ☑ A petition for an extension of time under 37 CFR 1.136(a) (PTO/SB/22) is enclosed.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 30,271
- ☐ attorney or agent acting under 37 CFR 1.34(a). Registration number if acting under 37 CFR 1.34(a). _____

Signature

Wayne M. Kennard

Typed or printed name

617-526-6183

Telephone number

4-7-04

Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

PTO/SB/22 (08-03)
Approved for use through 7/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARMENT OF COMMERCE

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a)

Docket Number 42697.265

In re Application of Eugene Shaknovich et al.

Application Number 09/897,584 | Filed 06/29/2001

For System and Method for Structure-Based Drug Design That Inc

Art Unit 1631 | Examiner Cheyne Ly

This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application.

The requested extension and appropriate non-small-entity fee are as follows (check time period desired):

- ☐ One month (37 CFR 1.17(a)(1)) $_____
- ☐ Two months (37 CFR 1.17(a)(2)) $_____
- ☑ Three months (37 CFR 1.17(a)(3)) $ 950
- ☐ Four months (37 CFR 1.17(a)(4)) $_____
- ☐ Five months (37 CFR 1.17(a)(5)) $_____

☒ Applicant claims small entity status. See 37 CFR 1.27. Therefore, the fee amount shown above is reduced by one-half, and the resulting fee is: $_____.

☒ A check in the amount of the fee is enclosed.

☒ Payment by credit card. Form PTO-2038 is attached.

☒ The Director has already been authorized to charge fees in this application to a Deposit Account.

☑ The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number 08-0219.

I have enclosed a duplicate copy of this sheet.

I am the ☒ applicant/inventor.

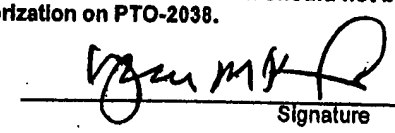
☒ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed (Form PTO/SB/96).

☒ attorney or agent of record. Registration Number 30,271

☒ attorney or agent under 37 CFR 1.34(a). Registration number if acting under 37 CFR 1.34(a) _____.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

4-7-05
Date


Signature

617-526-6183
Telephone Number

Wayne M. Kennard
Typed or printed name

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ Total of _____ forms are submitted.

PTO/SB/17 (10-03)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

FEE TRANSMITTAL for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 1,280.00

Complete If Known	
Application Number	09/897,584
Filing Date	06/29/2001
First Named Inventor	Eugene Shaknovich et al.
Examiner Name	Cheyne Ly
Art Unit	1631
Attorney Docket No.	42697.265

METHOD OF PAYMENT *(check all that apply)*

☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None

☑ Deposit Account:

Deposit Account Number: 08-0219

Deposit Account Name: Hale and Dorr LLP

The Director is authorized to: *(check all that apply)*

☑ Charge fee(s) indicated below ☑ Credit any overpayments

☑ Charge any additional fee(s) or any underpayment of fee(s)

☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1001	770	2001	385	Utility filing fee	
1002	340	2002	170	Design filing fee	
1003	530	2003	265	Plant filing fee	
1004	770	2004	385	Reissue filing fee	
1005	160	2005	80	Provisional filing fee	

SUBTOTAL (1) ($) 0.00

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

	Extra Claims		Fee from below		Fee Paid
Total Claims		-20** =		X	=
Independent Claims		- 3** =		X	=
Multiple Dependent			0		= 0

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description
1202	18	2202	9	Claims in excess of 20
1201	86	2201	43	Independent claims in excess of 3
1203	290	2203	145	Multiple dependent claim, if not paid
1204	86	2204	43	** Reissue independent claims over original patent
1205	18	2205	9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) ($) 0.00

**or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Large Entity Fee ($)	Small Entity Fee Code	Small Entity Fee ($)	Fee Description	Fee Paid
1051	130	2051	65	Surcharge - late filing fee or oath	
1052	50	2052	25	Surcharge - late provisional filing fee or cover sheet	
1053	130	1053	130	Non-English specification	
1812	2,520	1812	2,520	For filing a request for *ex parte* reexamination	
1804	920*	1804	920*	Requesting publication of SIR prior to Examiner action	
1805	1,840*	1805	1,840*	Requesting publication of SIR after Examiner action	
1251	110	2251	55	Extension for reply within first month	
1252	420	2252	210	Extension for reply within second month	
1253	950	2253	475	Extension for reply within third month	950.00
1254	1,480	2254	740	Extension for reply within fourth month	
1255	2,010	2255	1,005	Extension for reply within fifth month	
1401	330	2401	165	Notice of Appeal	330.00
1402	330	2402	165	Filing a brief in support of an appeal	
1403	290	2403	145	Request for oral hearing	
1451	1,510	1451	1,510	Petition to institute a public use proceeding	
1452	110	2452	55	Petition to revive - unavoidable	
1453	1,330	2453	665	Petition to revive - unintentional	
1501	1,330	2501	665	Utility issue fee (or reissue)	
1502	480	2502	240	Design issue fee	
1503	640	2503	320	Plant issue fee	
1460	130	1460	130	Petitions to the Commissioner	
1807	50	1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	1806	180	Submission of Information Disclosure Stmt	
8021	40	8021	40	Recording each patent assignment per property (times number of properties)	
1809	770	2809	385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	770	2810	385	For each additional invention to be examined (37 CFR 1.129(b))	
1801	770	2801	385	Request for Continued Examination (RCE)	
1802	900	1802	900	Request for expedited examination of a design application	

Other fee (specify) _____

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) ($) 1280.00

SUBMITTED BY

(Complete *(if applicable)*)

Name (Print/Type)	Wayne M. Kennard	Registration No. (Attorney/Agent)	30,271	Telephone	617-526-6183
Signature	Wayne M Kennard			Date	4-7-04

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Eugene Shaknovich et al.

Serial No. 09/897,584

Filed: 01/29/2001

For: SYSTEM AND METHOD FOR STRUCTURE-BASED DRUG DESIGN THAT INCLUDES ACCURATE PREDICTION OF BINDING FREE ENERGY

Examiner: Cheyne Ly
Art Unit: 1631

Reply

Sir:

This Reply is in response to the Office Action dated October 8, 2003.

Claims 1-4 are currently pending in the application, Applicants have reviewed the Examiner's bases for rejection of the application and set forth the following that traverses these rejections, thereby placing the present application in condition for allowance. Remarks/Arguments begin on page 2 of this paper.

Remarks

I. General

In the Office Action dated October 8, 2003, the Examiner rejected pending claims 1-4 on three bases. The first is under 35 U.S.C. § 112, first paragraph; the second is under 35 U.S.C. §102 for anticipation based on U.S. Patent No. 5,495,423 to DeLisi et at. ("DeLisi"); and the third is under 35 U.S.C. § 103 for obviousness base on DeLisi alone and DeLisi in view of U.S. Patent No. 6,251,620 to Hatada et al. ("Hatada"). Applicant will demonstrate that each of these bases for rejection is overcome and should be withdrawn, thereby placing the present application in condition for allowance.

Applicants would like to thank the Examiner for withdrawing the rejection associated with Applicants' claim of priority.

II. The Claims are Enabled by the Specification

The Examiner rejected claims 1-4 under 35 U.S.C. § 112, first paragraph on the basis that they are enabled for de novo design of molecules that interact with receptor sites of Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, or human carbonic anhydrase II protein, but not for the de novo design of molecules that interact with any receptor. The receptor sites that have just been recited are the preferred receptor sites. (See, Specification page 60, lines 8-11). These examples of receptor sites are the best mode for carrying out the invention at the time the application was filed.

The best mode and enablement requirements are two separate and distinct requirements under 35 U.S.C. § 112, first paragraph. *Teleflex, Inc. v Ficosa North America Corp.*, 299 F.3d 1313 (Fed. Cir. 2002). The best mode in the form of examples in the present application appear to be read by the Examiner as limitations to the scope of the claims and any receptor sites beyond them are not enabled. The case law, however, is clear that it is improper to limit the scope of claims to the preferred embodiment unless such a limitation is set forth in the specification or prosecution history. (See, *Northern Telecon Ltd. v. Samsung Electronics Co.*, Ltd., 215 F.3d 1281 (Fed. Cir. 2000); *TurboCare Division of Demag Delaval Turbomachinery Corp., v. General Electric Co.*, 264 F.3d 1111 (Fed. Cir. 2001)). Applicants have not so limited the claims and will have a scope that is supported by the specification beyond the preferred receptor sites.

The Specification at page 59, line 11 to page 60, line 8 describes the method of evaluating a receptor site for de novo design. Applicants describe at the bottom of page 22 and the top of page 23, that the crystalline structures of proteins and protein-ligands can be disassembled and the free energy contributions determined. This process is known and well within the capabilities of one skilled in the art without undue experimentation. Thus, the method of the present invention would result in the receptor sites that include but would not be limited to the preferred receptor sites Src-homology-3 domain, Src-homology-2 domain, MDM2 protein, CD4 protein, or human carbonic anhydrase II protein. Accordingly, the receptor sites that meet the criteria set forth by this method would be enabled by the disclosure of the present application beyond the preferred receptor sites. Thus, the pending claims are enabled by the specification beyond just the preferred receptor sites according to the disclosed method for evaluating the receptor sites to determine each's appropriateness for use. (See, *Mycogen Plant Science, Inc. v. Monsanto Co.*, 252 F.3d 1306 (Fed. Cir. 2001)). Accordingly, the enablement rejection has been traversed and should be withdrawn.

III. Claims 1-4 are not Anticipated

The Examiner has rejected claims 1, 3, and 4 under 35 U.S.C. §102 for anticipation based DeLisi. The Examiner contends that DeLisi teaches each and every element of the claims 1, 3, and 4 in the same way. Applicants submit that this error.

In the Applicants' previous amendment, the claims were amended to recite that the method uses "second generation molecules from one of more functional groups of the high-ranking molecules determined at Steps (a) and (b). The Examiner has contended that DeLisi discloses the use of second-generation molecules in its process. Applicants in the previous amendment stated that DeLisi does not teach or suggest the use of the second-generation molecules as set forth in the claims of the present invention.

The Examiner is hereby directed to Step (a) of claim 1 of the present application. At that step, the selection of fragments and their orientation is predicated on a free energy estimate that "may be higher than a lowest free energy estimate possible for the molecule." One the other hand, DeLisi builds molecules and selects fragments based on the minimum energy found and in no way contemplates the counterintuitive method of the present invention of using higher energy values in building first and second

generation molecules. Accordingly, DeLisi does not anticipate claim 1 of the present invention and this basis of rejection should be withdrawn.

Claims 3 and 4 depend from claims 1. Therefore, claims 3 and 4 add features to claim 1 and include claim 1's method of building molecules that use free energy estimates that may be higher than a lowest free energy estimate possible for the molecule. As such, these claims are not anticipated by DeLisi for the same reason claim 1 is not anticipated. Applicants, therefore, request that the anticipation rejection be withdrawn as it has been asserted against claims 3 and 4.

IV. Claims 1-4 are not Obvious

The Examiner has rejected claims 1, 3, and 4 under 35 U.S.C. §103 for obviousness based DeLisi. In view of *In re Gulack*, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983). The Examiner in applying *In re Gulack* to the DeLisi states that the case stands for defining that nonfunctional descriptive material will not distinguish the invention from prior art in terms of patentability. Although Applicants believe the Examiner was in error with regard to the conclusion reached regarding the distinguishing features of the "second generation molecule," Applicants want to point out, as was set forth in the previous section on anticipation, that claim 1 recites that the selection of fragments and their orientation is predicated on a free energy estimate that "may be higher than a lowest free energy estimate possible for the molecule." This is clearly not a "nonfunctional descriptive material" that distinguishes claim 1 from the Examiner's combination to form the rejection, but is clearly part of the defined claimed method for generating the first and second-generation molecules. Neither the combination of DeLisi and *In re Gulack* nor either of these references taken alone teach, suggest, or in any way render claim 1 obvious. Therefore, Applicants request the obviousness rejection be withdrawn as it has been applied to this claim.

Claims 2-4 depend from claim 1. These claims add features to claim 1 and include its method of building molecules that use free energy estimates that may be higher than a lowest free energy estimate possible for the molecule. Therefore, these claims are not rendered obvious by the DeLisi in view of *In re Gulack* for the same reason as claim 1 is not obvious. Applicants respectfully request that the obviousness rejection be withdrawn as it has been applied to claims 2-4 based on DeLisi in view of *In re Gulack*.